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Pharmaceuticals Inc.

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

July 19, 1999

Docket No. 99D-0674, Draft Guidance for Industry on INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products: Chemistry, Manufacturing and Controls Content and Format

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Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. wishes to provide the following general and specific comments on the subject draft Guidance for Industry.

General

1. The draft guideline refers in several places to the CMC requirements listed in FDA's Guidance for Industry, *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995). Since an IND may be opened at Phase 2 or Phase 3, it would be more helpful to describe the CMC requirements at these development stages rather than expecting the reader to refer back to the Phase 1 guideline.

   For example, in place of "changes to the information specified for Phase 1" or "updates on the information previously filed", please delineate the IND CMC content requirements for Phase 2 and Phase 3 INDs.

2. The concept of "safety-relevant" CMC information is a useful guide, but may be subject to different interpretation by different parties. Where possible, it would be helpful for the guideline to be more explicit as to what type and level of detail of CMC information is required to support Phase 2 and Phase 3 INDs.

99D-0674

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3. In some places, the draft guideline states that certain CMC data should be "available", or studies should be "conducted". It is not always clear from the language of the guideline, whether or not FDA expects these data to be submitted to the IND, or is simply providing more general advice.

Comments on Specific Sections

Section IIIA.4. Reference Standard

- Lines 170 to 174

The term "working standard" has been defined differently in other regulatory guidelines. For example a "working standard", as defined by FDA's *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987), is a is a reference standard used for routine laboratory analysis, qualified against a "[primary] reference standard".

We suggest the term "development reference standard" to describe an early reference standard, which may or may not ultimately become qualified and established as the "primary reference standard". A "working standard' is then qualified versus the primary reference standard.

Please also note that the draft ICH Guideline (Q7) ICH *GMP Guide for Active Pharmaceutical Ingredients* uses the term "secondary standard" to describe the same concept as a "working standard". It would be helpful to harmonize on one term, either "working standard" or "secondary reference standard" to avoid confusion.

Section IIIA.7. Stability

- Lines 213 – 214

Per the General Comment above, should the results of stress stability studies be submitted in support of a Phase 2 IND, or does the guidance simply recommend that these studies should be complete at this point in development?

- Line 220

The FDA's Phase 1 guideline mentions only stability data on "representative material". The statement in Line 220 appears to assume that the specific drug substance batch used in the Phase 1 dosage form, is on stability. This may not be the case, and we suggest this sentence be deleted.

Section IIIB.1. Component/Composition/Batch Formula

- Line 234 – 235

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We suggest that the Batch Formula be given in Section IIIB.4 where it is more easily understood in relation to the method of manufacture. This section would then be renamed Component/Composition.

Section IIB.2 Specifications for Components

- Lines 245 – 246

Please clarify for noncompendial excipients that a full description of the analytical procedures is not required, and that a reference to the type of procedure (*e.g.*, HPLC) may be provided.

Section IIB.4 Method of Manufacture, Packaging and Process Controls

This section does not appear to require the submission of information on the packaging operation. Therefore, we suggest that the word "Packaging" be deleted from the name of the section.

- Line 258

We suggest replacing the words "unit dose" with "drug product".

Section IIB.7 Stability

- Lines 304 – 305

Is submission ~~of~~ stress stability data on the drug product required for a Phase 2 IND, or is this a general recommendation that the studies should be done at this point in development?

Section IVA.4. Reference Standard

Same comments as above for Section IIIA.4. Reference Standard concerning terminology for the reference standards.

Section IIVB.1. Components, Composition, and Batch Formula

We suggest that the Batch Formula be given in Section IVB.4 where it is more easily understood in relation to the method of manufacture. This section would then be renamed Component/Composition.

Thank you for the opportunity to provide input on this draft guidance. We hope that these comments are helpful.

Please contact the undersigned with any questions or comments pertaining to this submission.

Boehringer Ingelheim

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs

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